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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,586	12/12/2005	Gabriele Multhoff	KNAUTHE-09734	3810

72960 7590 12/29/2008

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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
12/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,586	MULTHOFF, GABRIELE	
	Examiner	Art Unit	
	ANDREW D. KOSAR	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments/Arguments

Applicant's amendments and arguments filed July 14, 2008 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below in original or modified form is herein withdrawn.

It is noted that Applicant's amendments to the claims were not fully compliant, as claim 29 was amended without showing the changes. Specifically, steps (a) - (c) were changed to (b)-(d) without indicating the change. In the interest of compact prosecution, the amendment has been accepted as compliant, however this does not relieve Applicant of properly amending the claims in the future.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 25-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue',

not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to treating (a) viral infections, (b) bacterial infections, (c) inflammatory diseases or (d) a tumor comprising administering Granzyme B. Thus, the claims taken together with the specification imply one could treat any viral or bacterial infection, inflammatory disease or tumor via administration of granzyme B.

(3) The state of the prior art, (4) the predictability or unpredictability of the art and (5) the relative skill of those in the art:

The art recognizes that granzyme B is an endogenous protein and recognizes the apoptotic properties of granzyme B in the presence of perforin (e.g. Shi, et al. J. Exp. Med. (1997) 185(5), pages 855-866; IDS 10/12/07). The art additionally recognizes that granzyme B "enters cells without perforin and the addition of perforin had little effect on cytoplasmic levels of GraB in YAC-1 or HeLa cells." (Shi, page 864). Further, Shi teaches that GraB injected

directly into the cytoplasm of B16 melanoma cells "induced transient plasma membrane blebbing and nuclear coarsening but the cells did not become frankly apoptotic unless perforin was added." (Summary, page 855).

Further, Trapani (Trapani and Sutton. Curr. Opin. Immunol. (2003) 15, pages 533-543) provides that soluble granzymes (A and B) are found in serum and synovial fluid during acute exacerbations of RA and has been found in the acute phases of EBV and HIV infections and in Gram negative septicemia (page 540). Trapani further states, "Although there is no doubt that perforin plays a key role in the immune surveillance of cancer in several strains of mice, the contribution of granzyme A and B to protection against cancer is less clear." (page 540). Additionally, the NK-sensitive tumor cell like RMA-S required perforin, "but neither granzyme A or B. Conflicting results, however, have recently been reported by Simon and colleagues, who used a very similar *in vivo* tumor model. The reason for this discrepancy requires clarification and is currently under investigation." (page 540). Further, "The role of granzyme B and PI-9 in human malignancy is even more controversial. Although it has been shown previous that ectopic PI-9 expression in tumor cell lines can protect against purified granzyme B and perforin, and intact CLs *in vitro*, we urge extreme caution when extrapolating these findings to human disease." (page 540).

In Applicant's remarks in response to the anticipatory rejection, Applicant contends that they have "proceeded contrary to the accepted wisdom in the art." (Page 7). Applicant asserts that "the accepted wisdom in the art, as evidenced by Trouet I and II, is that granzyme B in it's mature form cannot be taken up by cells." (page 7).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

In relation to the claims, the specification provides an *in vitro* example of granzyme B inducing apoptosis in a single colon cancer cell line (example 4 of 5), however the specification fails to provide guidance as to how one would extrapolate the teaching to treating any viral or bacterial infection, inflammatory disease or tumor via administration of granzyme, particularly in view of the art cautioning against "extrapolating these findings to human disease." Additionally, the specification fails to provide any nexus between the *in vitro* colon cell line experiment and the myriad of conditions embraced by the claims, e.g. HIV, and fails to provide guidance as to how one would extrapolate the *in vitro* results to treating the myriad of other conditions, e.g. HIV.

Further, the specification fails to provide guidance as to how one would overcome the art recognition that granzyme B enters cells in the absence of perforin, that is alone (as instantly claimed), yet does not induce apoptosis until perforin in administered. Thus, the specification fails to provide sufficient guidance as to how one would induce apoptosis in the absence of an essential cofactor, such as perforin.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to granzyme B entering the cells in the absence of perforin and not inducing apoptosis, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANDREW D. KOSAR whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Andrew D Kosar/
Primary Examiner, Art Unit 1654